Approval Package for:

Application Number: 040212

Trade Name: ESTRADIOL TABLETS USP

Generic Name: Estradiol Tablets USP 0.5mg, 1mg 1,5mg

and 2mg

Sponsor: Duramed Pharmaceuticals, Inc.

Approval Date: December 29, 1997

APPLICATION 040212

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Application Number 040212

APPROVAL LETTER

Duramed Pharmaceuticals, Inc. Attention: John Rapoza 5040 Lester Road Cincinnati, OH 45213

Dear Sir:

This is in reference to your abbreviated new drug application dated October 4, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estradiol Tablets USP, 0.5 mg, 1 mg, 1.5 mg and 2 mg.

Reference is also made to your amendments dated October 17 and 24, and November 4, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Estradiol Tablets USP, 0.5 mg, 1 mg and 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Estrace Tablets 0.5 mg, 1 mg, and 2 mg, respectively, of Bristol Myers Squibb Company Pharmaceutical Research Institute). In addition, your Estradiol Tablets USP, 1.5 mg, can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CAR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

/S/

12/29/97

Douglas L. Spo**#**n

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

APPLICATION NUMBER 040212

FINAL PRINTED LABELING

PRESCRIBING INFORMATION

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

ENUIME INIAL CARLINUMA IN PUSINEMUPAUSAL WUMEN.

Close clinical surveillance of all women taking estrogens is important.

Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that 'natural' estrogens are more or less hazardous than synthetic' estrogens at equi-estrogenic doses.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engogenemen.

for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the letus, and possibly other birth defects. Studies of women who received diethy/istibestroi (DES) during pregnancy have shown that lemale offspring have an increased risk of vaginal adenosis, solutionary of the studies of the utility of cervix, and clear cell vaginal cancer later in life. The 1995 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of preast cancer later in interes, attnough a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

Estradiol (17 β -estradiol) is a white, crystalline solid, chemically described as estra-1.3.5(10)-tnene-3.17 β -diol, it has a molecular formula of $C_nH_nO_n$ and molecular weight of 272.39. The structural formula is:

Estradiol tablets, USP for oral administration, contains: 0.5 mg, 1 mg, 1.5 mg, or 2 mg of micronized estradiol per tablet.

Estradiol tablets. USP 0.5 mg contain the following inactive ingredients: lactose mono-hydrate, croscarmeilose sodium, carboxymethylcellulose sodium pregelatinized starch, magnesium stearate, polysorbate 80, FD&C Blue No. 1 Aluminum Lake, D&C Red No. 27 Aluminum Lake.

Estradiol tablets. USP. 1 mg contain the following inactive ingredients: lactose mono-hydrate, croscarmellose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium stearate, polysorbate 80, D&C Red No. 27 Aluminum Lake. Estradiol tablets. USP. 1,5 mg contain the following inactive ingredients: lactose mono-hydrate, croscarmellose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium stearate, polysorbate 86, FD&C Blue No. 1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake.

Statedio Italieis. USP 2 mg contain the following inactive ingredients: lactose monohydrate, croscarmellose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium stearate, FD&C Blue No. 2 Atuminum Lake, polysorbate 80.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor. a DNA-binding protein which is found in estrogen-responsive itssues. The activated estrogen receptor binds to specific DNA sequences, or hormone-responsive telements, which enhance the transcription of adjacent genes and in Jun lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, nuturally hypothalamus, liver, and bone of women.

hypothalamus, liver, and bone of women.

Estrogens are important in the development and maintenance of the lemale reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus, Fallopian tubes, and vagina. With other hormones such as pit, tarry hormones and progesterione, they cause enlargement of the breasts through promotion of ducta growth, stromal development, and the accretion of fat. Estrogens are intricately involved with other hormones, especially progesterione, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pitulary ponadotropins. They also contribute to the shaping of the skeleton, maintenance of tone and elasticity of unogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, and pigmentation of the ripples and gentals.

mentation of the nipples and gentals.

Estrogens occur naturally in several forms. The primary source of estrogen in organization of the primary source of estrogen in organization of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and is small amounts of estroid. Her menopause, most endogenous estrogen is produced by comversion of androsstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its suitate ester form—is the most abundant circulating estrogen in postmenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estroid at the receptor.

estrone or estimate the receptor. Estropen used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with arryl and alkyl groups for parenteral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cypionate is absorbed over several weeks.

valerate or estradiol cypionate is absorbed over several weeks.

Administered estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabolic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dyname equilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted. especially estewen eststone and estradiol and between estertified and non-esteritied forms. Although naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, brily unbound estrogens enter target tissue cells. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogenic sextend into the bite and their reabsorbed from the intestine. During this enterohepatic recirculation, estrogenic are desulfated and resulfated and undergred degradation through conversion to less active estrogens (estroil and other estrogens), oxidation to nonestrogenic substances (catechoolestrogens, which interact with catecholamine metabolism especially in the central nervous system), and conjugation with glucuronic acids (which are then reapidly excreted in the uring).

(which are then rapidly excreted in the unne). When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone suitate, with smaller amounts of other conjugated and unconjugated estrogens, especies. This results in emitted oral polaricy, by contrast, synthetic estrogens, such as ethinyl estration and the finitiverniqual estrogens, are degraded very slowly in the liver and other insues which results in which right intrinsic potency. Estrogen drug products administered by non-oral routes are not suivect to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and vertoringate recycling.

INDICATIONS AND USAGE

Estradiol tablets. USP are indicated in the

ESTRADIOL TABLETS, USP



FSTRADIOL TABLETS, USP



ESTRADIOL TABLETS, USF Fydrafe, croscarmenose sodium, carboxymetnyiceninesc sodium, pregeratimized starch, magnesium stearate, polysorbate 80, D&C Red No. 27 Aluminium Lake

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Estradiol tablets. USP. 2 mg contain the following inactive ingredients: lactose mono-hydrate, croscarmeliose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium stearate, FD&C Blue No. 2 Aluminum Lake, polysorbate 80.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell mempranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-responsive insistes. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, which enhance the transcription of adacent genes and in turn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, branch invalidation, invalidation, invalidation, invalidation, production in the productive tract, branch in the productive tract, branch

hypothalamus, liver, and bone of women. Estrogens are important in the development and maintenance of the lemaie reproduc-bive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus. Fallopian tubes, and vagina. With other hormones, such as piticitary hormones and progesterione, they cause enlargement of the breasts the processes of the ordinary production of ductar growth, stromal development, and the accretion of fall. Estrogens are intricately involved with other hormones, sepecially progesterone, in the processes of the ovulatory mensitual cycle and pregnancy, and affect the release of pitulary gonadotropins. They also contribute to the shaping of the skeletion, main-tenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and ris termination, and pig-mentation of the nipples and genitals.

mentation of the nipples and genitals. Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estroil. After menopause, most endogenous estrogen is produced by conversion of androsinaedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone—especially in its suitate ester form—is the most abundant circulating estrogen is prostingens estroned in the principal intracellular human estrogen and is substantially more potent than estrone or estroil at the receptor.

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INDICATIONS AND USAGE

Estradiol tablets, USP are indicated in the

- Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
- Treatment of vulval and vaginal atrophy
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
- Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
- Treatment of advanced androgen-dependent carcinoma of the prostate (for pallia-tion only).
- Prevention of osteoporosis.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection

endometrial cancer (see Boxed Warnings). Estrogen replacement therapy reduces bone resorption and retards or haits postmenopausal bone loss. Case-control studies have shown an approximately 60 percent
reduction in hip and wrist tractures in women whose estrogen replacement was
begun within a tew years of menopause. Studies also suggest that estrogen reduces
the rate of vertebral fractures. Even when started as late as 6 years after menopause,
estrogen prevents further loss of bone mass for as long as the treatment is continued. The results of a lwo-year, randomized, placebo-controlled, double-blind study
have shown that treatment with 0.5 mg estradiol daily for 23 days (of a 28 day cycle)
prevents vertebral fractures. When estrogen therapy is discontinued, bone mass
declines at a rate comparable to the immediate postmenopausal period. There is no
evidence that estrogen replacement therapy restores bone mass to premenopausal
levels.

At skeletal maturity there are sex and race differences in both the total amount of bone present and its density, in favor of men and blacks. Thus, women are at higher risk than men bust they start with less bone mass and, for several years following natural or induced menopause, the rate of bone mass decline is accelerated. White and Asian women are at higher risk than black women.

and Asian women are at higher risk than black women.

Early menopause is one of the strongest predictors for the development of oseophorosis. In addition, other factors affecting the skeleton which are associated with
osteoporosis include genetic factors (small build, family history), endocrine factors
(nullipairit), hyprotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperporlactinemia, Type I diabetes), lifestyle (cigarette smoking, alcohol abuse, sedentary
exercise habits) and nutrition (below average body weight, dietary calcium intake).

The mainstays of prevention and management of osteoporosis are estrogen, an adequate lifetime calcium intake, and exercise. Postmenopausal women absorb dietary
calcium less efficiently than premenopausal women and require an average of 1500
mg/day of elemental calcium to remain in neutral calcium balance. By comparison,
premenopausal women require about 1000 mg/day and the average calcium intake in
the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be helpful.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention.

Meight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

- Known or suspected pregnancy (see Boxed Warning). Estrogens may cause fetal harm when administered to a pregnant woman.
- Undiagnosed abnormal genital bleeding.
- Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
- Known or suspected estrogen-dependent neoplasia
- Active thrombophlebitis or thromboembolic disorders.

WARNINGS

Induction of malignant neoplasms.

Induction of malignant neoplasms.

Endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens are shown on the preatest risk appears associated with prolonged use—with increased risks of 115 to 24-fold for five to ten years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessand of estrogen treatment. In one study a significant decrease in the michaero of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see Precautions).

See Precadiums).

Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years, Other studies have not shown this relationship.

cially in excess of 10 years, Other studies have not shown this relationship.

Congenital leations with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth detects. Studies of women who received buring pregnancy have shown that temale offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear vaginal adenosis rater in life, male offspring have an increased risk of urogenital abnormalities and possibly texticular caneur later in life. Although some of these changes are benign, others are precursors of malignancy.

- Gallbladder disease. Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal
- estrogens.

 Cartifurgacular disease. Large doses of estrogen (5 mg conjugated estrogen per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary, embolism, and thrombophilebitis. These risks cannot necessarily be estrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen defective dose.
- Elevated blood pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure among estrogen users compared to nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not not provide the provided to nonusers. Postmenopausal estrogen use does not regular intervals with estrogen use.
- Hypercalcemia. Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the ser

PRECAUTIONS

Addition of a progestin. Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:

- (1) adverse effects on ipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS below):
- (2) impairment of glucose tolerance; and

A. General

(3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see PRECAUTIONS below).

The choice of progestin, its dose, and its regimen may be important in mini-mizing these adverse effects, but these issues will require further study before

Cardiovascular risk. A Gausal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenorausal women has not been proven. Furthermore, the effect of added propestins on this putative benefit is not yet known.

tottam is not post inform.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy <u>without added progestins</u> and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% control of the cont

unknown, available epidemiological evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS above).

ment therapy (see wanning) agove).

Because relatively long-term use of estrongrs by a woman with a uterus has been shown to induce andometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take propositions as well as estrogens. When considering respirating concomitant estrogens are propositins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added proposition. Large-state randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

- 3. Physical examination. A complete medical and tamily history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure. breasts, abdomen. and perior organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

 4. Humanagamulabilitie. Some studies have shown that woman taking estrogen.
- for longer than one year without reexamining the patient.
 Hyperceaguiability. Some studies have shown that women taking estrogen replacement therapy have hyperceaguiability, primarily relate decreased antitinombin activity. This effect appears dose- and duration-dependent and ises pronounced than that associated with ord ourstion-dependent and ises pronounced than that associated with our contraceptive use. Also, postmenopausal women tend to have increased coaguiation parameters at asseline compared to premenopausal women. There is some suggestion that low dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (of primarily conjugated estrogens users) report no such increase. There is insufficient information in hypercoagulability in women who have had previous thromboembolic disease.
- Familial hyperipoproteinemia. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
- Fluid retention. Because estrogens may cause some degree of fluid reten-tion, conditions which might be exacerbated by this factor, such as sathma, epilepsy, migraine, and cardiac or renal dysfunction, require care-ful observation.
- **Uterine bleeding and mastodynia.** Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.
- Impaired liver function. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.
- Information for the Patient, See text of Patient Package Insert below
- Intulnation for the Fategin, See text or Fategin Fateging Interface to California (Laboratory Lests, Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention and treatment of osteoporosis however, see Dosage and Administration cartion.

D. Drug/Laboratory Test Interactions.

- Accelerated protrinombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII catquiant activity, IX, X, XII, VIII-X complex, III-VIII-X complex, and beta-thromboglobulin; decreased elvels of anti-factor Xa and antithrombin III, decreased antithrombin III activity, increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PB), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and tree T3 concentrations are unaltered.
- Concentrations are untainered. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CHBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, cerulo-
- Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test
- 7. Reduced serum folate concentration.
- Carcinogenesis. Mutagenesis. Impairment of Fertility. Long term continuous administration of natural and symbotic weighten in certain animal species for requency of acartinomas of passes, uterus, course, species testis, and liver. See Contraindications and Warnings.
- Pregnancy Category X. Estrogens should not be used during pregnancy. See Contraindications and Boxed Warning.
- Contrainmentations and doese Perinning.

 Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.
- nig motivers has been shown to decrease the quantity and quanty in the mine. <u>Pediatric_Use</u>: Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not com-plete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (see Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of palibladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia)

- Genitourinary system
 Changes in vaginal bleeding pattern
 and abnormal withdrawal bleeding
 or flow, breakhrough
 bleeding, spotting,
 increase in size of uterine
 telomyomata.
 Vaginal candidiasis.
 Change in amount of cervical
 secretion.
- <u>Breasts</u> Tenderness, enlargement.
- Gastrointestina! lausea, vomiting. Abdominal cramps, bloating. Cholestatic jaundice. Increased incidence of galibladder disease.
- Skin Chloasma or melasma that may persist when drug is discontinued.
- Eyes Steepening of corneal curvature. Intolerance to contact lenses.
- Central Nervous System
 Headache, migraine, dizziness.
 Mental depression.
- Miscellaneous
 Increase or decrease in weight.
 Reduced carbohydrate tolerance.
 Aggravation of porphyria.
 Edema. Changes in libido

one study a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known

Breast Cancer. While the majority of studies have not shown an increased risk of

cially in excess of 10 years. Other studies have not shown this relationship.

Congenital lexions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who received DES during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cencer later in life, male obstiguita cancer later in life, male obstiguitar cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

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- estrogers.

 Cardiovapeular disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to, those used to treat cancer at the prostate and breast, have been shown in a large prospective clinical rial in men to increase the risks of nonitatal myocardial instanction, pulmonary embolism, and thrombophilebits. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estimated doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.
- effective dose

 Elevated blood pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.
- Hypercalcemia. Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

A. General

Addition of a progestin. Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:

- (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS below);
- (2) impairment of glucose tolerance; and
- (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see PRECAUTIONS below).

The choice of progestin, its dose, and its regimen may be important in mini-mizing these adverse effects, but these issues will require further study before

Cardiovascular risk. A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added propestins on this putative benefit is not yet known.

benefit is not yet known.

In recent years many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added nonpestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

- (1) Because only one of these studies was randomized and it was too small to Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy, it may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more stender, more hysically active, more likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.
- (2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heard disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.
- (3) While the effects of added progestins on the risk of breast cancer are also

- Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloolasmin).
- Increased plasma HDL and HDL-2 subtraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
- Impaired alucose tolerance
- Reduced response to metyrapone test.
- Reduced serum folate concentration.
- Carcinogenesis. Mutagenesis. Impairment of Fertility. Long term continuous administration of natural and synthetis extrogens in certain animal species increases the frequency of accrinomas of the oreast, uterus, Lerya, Veynactesis, and liver. See Contraindications and Warnings.
- Pregnancy Category X, Estrogens should not be used during pregnancy. See Contraindications and Boxed Warning.
- Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphyseal closure, resulting in short adult sature it treatment is initiated before the completion of physiologic puberty in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in glirs. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (see Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of galibladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia).

- Genitourinary system Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough or flow; breakthrough bleeding, spotting. Increase in size of uterine leiomyomata. Vaginal candidiasis. Change in amount of cervical secretion.
- Breasts Tenderness, enlargement.
- Gastrointestinal Nausea, vomiting Abdominal cramps, bloating Cholestatic jaundice Increased incidence of gallbladder disease.
- Skin Chloasma or melasma that may persist when drug is discontinued Erythema multiforme Erythema nodosum Erythema nodosum. Hemorrhagic eruption. Loss of scalp hair. Hirsutism.

- 5. Eyes Steepening of corneal curvature intolerance to contact lenses
- Central Nervous System
 Headache, migraine, dizziness
 Mental depression.
- 7. Miscellaneous Inscendieus
 Inscendieus
 Inscende de decrease in weight.
 Reduced carbohydrate toleranci
 Aggravation of porphyria.
 Edema. Changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

Estradiol tablets, USP

For treatment of moderate to severe vasomotor symptoms, vulval and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discertificated as promptly as possible.

Attempts to discontinue or taper medication should be made at 3-month to 6-month intensity.

month intervals.

The usual initial dosage range is 1 to 2 mg daily of estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Administration should be cyclic (e.g., 3 weeks on and 1 week off).

For treatment of female is or primary evertee failure.

Treatment is usually initiated with a dose of 1 to 2 mg daily of estradiol adjusted as necessary to control Presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.

For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease.
 Suggested dosage is 10 mg three times daily for a period of at least three months.

For treatment of advanced androgen-dependent carcinoma of the prostate,

For transfer or sevantees and very seven s improvement of the patient.

For prevention of osteoporosis.

Therapy with Estradiol tablets, USP to prevent postmenopausal bone loss should be initiated as soon as possible after menopause. A daily dose of 0.5 mg should be administered cyclically (i.e., 23 days on and 5 days off). The dosage may be adjusted if necessary to control concurrent menopausal symptoms. Discontinuation of estrogen replacement therapy may re-establish the natural rate of bone loss

HOW SUPPLIED

Estradiol tablets, USP 0.5 mg; round, lavender colored tablet with bisect, debossed with $\frac{4}{9}$ and 501. Available in containers of 30 (NDC 51285-501-30), 100 (NDC 51285-501-02). and 500 (NDC 51285-501-04).

Estradiol tablets, USP 1 mg, round, rose colored tablet with bisect, debossed with \$\frac{4}{9}\$ and 502. Available in containers of 30 (NDC 51285-502-30), 100 (NDC 51285-502-02), and 500 (NDC 51285-502-04).

Estradioi lablets, USP 1.5 mg; round, aqua colored tablet with bisect, debossed with \$\frac{4}{3}\$ and 503. Available in containers of 30 (NDC 51285-503-30), 100 (NDC 51285-503-02) and 500 (NDC 51285-503-04).

Estradiol tablets, USP 2 mg; round, blue colored tablet with bisect, debossed with \$4 and 504. Available in containers of 30 (NDC 51285-504-30), 100 (NDC 51285-504-02), and 500 (NDC 51285-504-04).

Store at controlled room temperature 15°-30°C (59°-86°F)

INFORMATION FOR THE PATIENT

INTRODUCTION

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

estrogen readment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend upon the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE").

If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during preg-nancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they

HISES OF ESTROGEN

(Not every extrogen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physicians" besk Reference" which is available in many book stores and public libraries. Generic drugs carry virtually the same tabeling information as their brand name versions.

To reduce mederate or severe menopausal symptoms. Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the 'change of life' or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".

causes 'surgical menopause'. When the estropen fevels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episbles of neat and seveating ("hot flashes" or "hot flushes"). Using estropen drugs can help the body adjust to lower estropen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estropen drugs for these symptoms. Others may need to take estrogens for a tew months while their bodies adjust to lower estropen levels. The majority of women do not need estropen replacement for longer than six months for these symptoms.

- Te treat valval and vaginal atrophy (titching, burning, dryness in or a the vagina, difficulty or burning on urination) associated with menopaus
- To treat certain conditions in which a young woman's ovaries do not produce enough extregen naturally.
- To treat certain types of abnormal vaginal bleeding due to hormenal imbalance when your doctor has found no serious cause of the bleeding.
- To treat certain cancers in special situations, in men and women.

To prevent thinking of bones.

To prevent thinning of bones.

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Butter descriptions after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium Intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like weaking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium Intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During pregnancy (see Boxed Warning).
If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to

When they do net work.

During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen

After childhirth or when breastleading a baby. Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see Dangers of Estrogens, below).

If you are breastfeeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

Cascar of the uterus.

Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayde high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see Other Information, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Center of the bresst.

Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

Galibladder disease.

Women who use estrogens after menopause are more likely to develop gallblad-der disease needing surgery than women who do not use estrogens.

der disasse needing surjery man women wind on not use estrugeris.

Aharman blood lebtling.

Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream, they can cut off the blood supply to vital organs, causing senious problems. These problems may include a stroke (by cutting off blood to the heart), a pulmonary embolus (by cutting off bl show an increased risk of these complication

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus

Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things

See your decire regularly.

While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast jumps or an abnormal mammogram (breast x-ray). you may need to have more frequent breast examinations.

Reassess your need for extrogens.
You and your doctor should reevaluate whether or not you still need estrogens at

Be alert for signs of trouble.

If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

Abnormal bleeding from the vagina (possible uterine cancer)

Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eve)

Breast lumps (possible breast cancer, ask your doctor or health professional to show you how to examine your breasts monthly)

Yellowing of the skin or eyes (possible liver problems)

Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

Estrogens increase the risk of developing a condition (endometrial hyperpla-sia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this con-dition. Therefore, it your uterus has not been removed, your doctor may pre-scribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken <u>without</u> progestins may pro-tect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estro-pen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- If you will be taking calcium supplements as part of the treatment to help pre-vent osteoporosis, check with your doctor about how much to take.
- Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
- This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labelling. The professional labelling is also published in a book called the "Physicians" besk Reference, "which is available in book stores and public libraries. Generic drugs carry virtually the same labelling information as their brand name versions. information as their brand name versions

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During pregnancy (see Boxed Warning).
If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

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If you have unusual vaginal bleeding which has not been evaluated by your dector (see Boxad Warning).

Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have had cancer.

If you have hall cancer.

Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For cartain patients with breast or prostate cancer, estrogens may help.)

Patients with the ast product would be used except in unusually special situations in Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see Dangers of Estrogens, below).

If you use estrogens, you can reduce your risks by boing these things

See your doctor regularly.

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While you are using estrogens, it is important to visit your doctor at least once a war for a check-up. If you develop valinal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or you have ever had breast lumps of an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

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Be afert for signs of trouble

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Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)

Yellowing of the skin or eyes (possible liver problems)

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You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- If you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.
- Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
- This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reterence," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

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100304

Manufactured by: Duramed Pharmaceuticals, Inc. Cincinnati, DH 45213 USA

CAUTION: Federal law prohibits dispensing without prescription

DURAMED PHARMACEUTICALS, INC. CINCINNATI, DHIO 45213 U.S.A.

Iss. 9/97

PRESCRIBING INFORMATION

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.

Close clinical surveillance of all women taking estrogens is important Adequate diagnostic measures, including andometrial sampling when indi-cated, should be undertaken to rule out malignancy in all cases of undag-nosed persistent or recurring abnormal vaginal bleeding. There is no evi-dence that "natural" estropens are more or less hazardous than "synthetic" estropens at equi-estropenic doses.

ESTROGERS SHOULD NOT BE USED DURING PREGNANCY.

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

For the prevention of postpartum brasst engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the lettus, and possibly other birth detects. Studies of women who received diethylsidestrol (DES) during pregnancy have shown that ternale offspring have an increased risk of vaginal adenosis. squamous cell dysplasia of the uterna cervix, and clear cell vaginal cancer later in life, male offspring have an increased risk of urgential abnormatities and possibly testicular cancer later in life. The 1985 DES Task force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

Estradiol (17p-estradiol) is a white, crystalline solid, chemically described as estra-1.3.5(10)-triene-3.17p-diol. It has a molecular formula of C_wH_xO_x and molecular weight of 272.39. The structural formula is:

is, USP for eral administration, contains: 0.5 mg, 1 mg, 1.5 mg, or 2 mg

Estradiol lablets. USP 0.5 mg contain the following inactive ingredients: lactose mono-hydrate, croscarmellose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium stearate, polysorbate 80, FD&C Blue No. 1 Aluminum Lake, D&C Red No. 27 Aluminum Lake.

Estradiol tablets. <u>USP. 1 mg</u> contain the following inactive ingredients: lactose mono-hydrate, croscarmellose sodium, carboxymethylicellulose sodium, pregelatinized starch, magnesium stearate, polysorbate 80, D&C Red No. 27 Aluminum Lake. Estradiol tablets, USP, 1 mg contain the tollow

Estination tables. ISEP 1.5 mg contain the following inactive ingredients: lactose monohydrate, croscarmeitose sodium. carbosymethylcellulose sodium, pregelatinized starch, magnesium stearate, polysorbate 8), FD&C Blue No. 1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake, D&C

Estradiol tablets. USP 2 mg contain the following inactive ingredients: lactose mono-hydrate, croscarmellose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium stearate, FD&C Blue No. 2 Aluminum Lake, polysorbate BO.

CLINICAL PHARMACOLOGY

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein which is found in estrogen-response tissues. The activated estrogen receptor binds to specific DNA sequences, or homome-response elements, which enhance the transcription of adjacent genes and in urn lead to the observed effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, privmenry, hypothalamus, liver, and bone of women.

hypothalamus, liver, and bone of women. Estropens are important in the development and hairtenance of the female reproductive system and secondary sex characteristics. By a direct action, they cause growth and development of the uterus. Fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progestrone, they cause entergement of the breasts through promotion of ductal growth, stromal development, and the accretion of tat. Estropens are intricately involved with other hormones, especially progestrone, in the processes of the orulatory menstruial cycle acd pregnancy, and affect the release of phuldary pondetropies. They also contribute to the shaping of the skelerion, maintenance of tone and dissticity of urogenital structures, changes in the epiphyses of the long bones that allow for the puberfal growth spurt and its termination, and pigmentation of the nipples and genitals.

mentation of the nippies and gentals. Estrogens occur naturally in several forms. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarity to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estroil. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone — especially in its sulfate ester form — is the most abundant circulating estrogen in opstimenopausal women. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than estrone or estroil at the receptor.

estrone or soutle at one receptor.

Estrogens used in therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. When applied for a local action, absorption is usually sufficient to cause systemic effects. When conjugated with any and ally groups for parentaral administration, the rate of absorption of oily preparations is slowed with a prolonged duration of action, such that a single intramuscular injection of estradiol valerate or estradiol cyplorate is absorbed over several weeks.

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Administrated estrogens and their esters are handled within the body essentially the same as the endogenous hormones. Metabloic conversion of estrogens occurs primarily in the liver (first pass effect), but also at local target tissue sites. Complex metabolic processes result in a dynamic aguilibrium of circulating conjugated and unconjugated estrogenic forms which are continually interconverted, especially between estrone and estradiol and between estertied and non-esteritied forms. Atthough naturally-occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin, only unbound estrogens enter target tissue calls. A significant proportion of the circulating estrogen exists as sulfate conjugates, especially estrone suifate, which serves as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogenic specially estrone suifate, which serves as a circulating reservoir for the formation of the blue and then reabsorbed from the infestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo degradation through conversion to less active estrogens (estrol) and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism-especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly accreted in the urne).

(which are then rapidly excreted in the urine). When given orally, naturally-occurring estrogens and their esters are extensively metabolized (first pass effect) and circulate primarily as estrone suifate, with smaller amounts of other conjugated and unconjugated estrogens; especies. This results in limited oral potency. By contrast, synthetic estrogens, cate as ethinyle estradiol and the nonsteroidal estrogens, are degraded very slowly in the liver and other bissues, which results in their high intrinsic potency. Estrogen drug products administered by non-oral routes are not subject to first-pass metabolism, but also undergo significant hepatic uptake, metabolism, and enteronegatic recycling.

INDICATIONS AND USAGE





ES COL TABLES, USP



ES ASSOUL TABLE S, USP SEPARATE PHYSICIAN (TOP) AND PATIENT (BOTTOM) LEAVE PATIENT WITH BOTTLE ol mecronizad estradioi per tablet

Estración tables. USP 0.5 mg contain the following mactive ingredients: lactose mono-hydrate, croscarmellose sodium, carboxymethylcellulose sodium, pregelatinized starch, magnesium staarate, polysorbate 80, FD&C Blue No. 1 Aluminum Lake, D&C Red No. 27 Aluminum Lake.

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starcn, magnesium strairate, polysorbate au. valu new nu. 21 Automitant Lance.

<u>Estrairo Ishens. 1597. 1.5 mg</u> contain the following inactive ingredients: lactose monohydrate, croscarmellose sodium, carbolaymethylcellulose sodium, propelatinized
starch, magnesium staarate, polysorbate 80, FD&C Blue No. 1 Aluminum Lake. D&C
Yellow No. 10 Aluminum Lake.

Fatradiol tablets, USP. 2 mg contain the logowing mactive ingredients: tactose mono-hydrate, croscarmeliose sodium, carboxymethylcellulose sodium, prepetatinized starch, magnesium stearate, FD&C Blue No. 2 Aluminum Lake, polysorbate 80.

CLINICAL PHARMACOLOGY

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INDICATIONS AND USAGE

Estradiol tablets, USP are indicated in the:

- ESTABLION LAUREN, LOT are INJURIENCE at the.

 1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estropens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.
- 2. Treatment of vulval and vaginal atrophy.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovar ian failure.
- Treatment of breast cancer (for palliation only) in appropriately s and men with metastatic disease.
- Treatment of advanced androgen-dependent carcinoma of the prostate (for pallia-5. tion only)

O. Prevention to coreuporusas.

Since estrogen administration is associated with risk, selection of patients should ideally be based on prospective identification of risk factors for developing osteoporosis. Unfortunately, there is no certain way to identify those women who will develop osteoporotic fractures. Most prospective studies of efficacy for this indication have been carried out in white menopausal women, without stratification by other risk factors, and tend to show a universally salutary effect on bone. Thus, patient selection

t be individualized based on the balance of risks and benefits. A more favorable benefit ratio exists in a hysterectomized woman because she has go risk of metrial cancer (see Boxed Warnings).

endometrial cancer (see Board Warnings).

Estrogen replacement therapy reduces bone resorption and retards or halts postmenopausal bone loss. Case-control studies have shown an approximately 60 percent
reduction in hip and wrist fractures in women whose estrogen replacement was
begun within a few years of menopause. Studies also suggest that estrogen reduces
the rate of vertebral tractures. Even when started as late as 6 years after menopause
strogen prevents further loss of bone mass for as long as the treatment is contriued. The results of a two-year, randomized, placeob-controlled, double-bland study
have shown that treatment with 0.5 mg estradiol daily for 23 days (of a 28 day cycle)
prevents vertebral fractures. When estrogen therapy is discontinued, bone mass
declines at a rate comparable to the immediate postmenopausal period. There is no
evidence that estrogen replacement therapy restores bone mass to premenopausal
levets.

averse. At skeletal maturity there are sex and race differences in both the total amount bone present and its density, in favor of men and blacks. Thus, women are at high risk than men because they start with less borne mass and, for several years follow natural or induced menopeuse, the rate of bone mass deckine is accelerated. Wit and Asian women are at higher risk than black women.

and Again women are at name rask earn back, would be Early menopause is one of the strongest predictors for the development of osteo-porosis. In addition, other factors affecting the skeleton which are associated with osteoporosis include genetic factors (small build, family history), endocrine factors (nulliparity, thyrotoxicosis, hyperparathyroidism, Cushing's syndrome, hyperpo-sicinemia, Type I disablets), lifestyle (cigarette smoking, alcohol abuse, sedentary exercise habits) and nutrition (below average body weight, dietary calcium intake).

exercise reasons) and interiori (seem'exercise) over weight, ownerly calcium interior. The maintable of prevention and management of osteoprocess are estrogen, an adequate lifetime calcium intelle, and exercise. Postmenopausal women absorb dietary calcium less efficiently than preveneopausal women and require an everage of 1500 mg/day of elemental calcium to remain in neutral calcium balance. By comparison, preveneopausals women require about 1000 mg/day and the average calcium intelle in the USA is 400-600 mg/day. Therefore, when not contraindicated, calcium supplementation may be heightly.

Weight-bearing exercise and nutrition may be important adjuncts to the prevention and management of osteoporosis. Immobilization and prolonged bed rest produce rapid bone loss, while weight-bearing exercise has been shown both to reduce bone loss and to increase bone mass. The optimal type and amount of physical activity that would prevent osteoporosis have not been established, however in two studies an hour of walking and running exercises twice or three times weekly significantly increased lumbar spine bone mass.

CONTRAMINICATIONS

Estrogens should not be used in individuals with any of the following conditions:

- Known or suspected pregnancy (see Boxed Warning). Estrogens may cause fetal harm when administered to a pregnant woman.
- Undiagnosed abnormal genital bleeding.
- Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
- 4. Known or suspected estrogen-dependent neoplasia.
- 5. Active thrombophlebitis or thromboembolic disorders.

Redecentrial scarcer. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose, Most studies show no significant increased risk associated with use of estrogens for less than one year. The greates risk appears associated with protonged use — with increased risks of 15 to 24-fold for fire to ten years or more. In three studies, persistance of risk was demonstrated for 8 to over 15 years after estessation of extrogen treatment. In one study a significant decrease in the incidence of endometrial cancer occurred aix months after estrogen withdrawal. Concurrent progestin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see Prezentinis).

Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risks of 1.3-2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, espe-cially in excess of 10 years. Other studies have not shown this relationship.

cially in excess of 10 years. Other studies have not shown this relationship. Cempental lebelose with smallpassa petretals. Estrogen therapy during preg-nancy is associated with an increased risk of tetal congential reproductive tractions of the studies of women who received be during regnancy have shown that temale offspring have an increased risk of variety and the studies of the studies of women control and possibly testicular concer (rate in the Mesough some of these changes are benign, others are procursors of malignancy, and increased in the city.

- Ballbladder disease. Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surpery in women receiving postmenopausal extranens.
- Cardiovascular disease. Large doses of estrogen (5 mg conjugated estrogens Cardiovascelar diseases. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men do increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophiebits. These risks cannot necessarily 6e extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective force.
- 4. Elevated blood pressure. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Somenopausal estrogen users does not increase the risk of stroke. Bonetheless, blood pressure should be monitored at results interest with entropy less than the property of the property of the property of the pressure should be monitored at results interest with entropy less. regular intervals with estrogen use.
- Hypercalcomia. Administration of estrogens may lead to severe hypercalcomia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level

Addition of a progestin. Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplassis than would be induced by estrogen treatment alone. Morphological and blochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:

- adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS below);
- (2) impairment of glucose tolerance; and
- (3) possible enhancement of mitotic activity in breast epithelial tissue, although lew epidemiological data are available to address this point (see PRECAUTIONS below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. Cardiovascular risk. A causal relationship between estrogen replacement therany and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added propestins on this putative benefit is not yet known.

In mostry type sensing.

In mostry types manny published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added propestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in extrogen takers, the following should be considered when interpreting these reports:

(1) Recayse only one of these studies was randomized and it was too small to

unknown, available epidemiological evidence suggests that progestins do not ruduce, and may enhance, the moderately increased breast can-cer incidence that has been reported with prolonged estrogen replace-

Because relatively long-term use of estrogers by a woman with a uterus has been shown to induce endometrial cancer, obysicians often recommend that women who are deemed candidates for hormone replacement should take processors as well as estrocens. When considering prescribing concomitant extrocens and processins for hormone replacement therapy, physicians and nations are advised to carnituly wealth the nestimal benefits and issues of the added procession. Largestrolled, prospective clinical trials are required to

- Physical Establishment A complete medical and tamily history should be taken prior to the indication of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolacou smear. As a general rule, estrogen should not be prescribed for longer than one year without resignmining the patient. 3. Physical exem
- Hyperessquiability: Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, is less pronounced man that associated with oral confraceptive use. Also postmenopausal women tend to have increased coagulation parameters a baseline compared to premenopausal women. There is some suggestion that low does postmenopausal mestranol may increase the risk of throm-boembolism, although the majority of studies (of primarily conjugate estrogens users) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboemboli-
- Familial hyperhaps rate/memia. Estrogen therapy may be associated with massive elevations of plasma triplycandes leading to pancreatitis and other complications in patients with familial detects of lipoprotein metabolism.
- Fluid retainties. Because estrogens may cause some degree of fluid reten-tion, conditions which might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require care-
- Uterine biseding and mastedynia. Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine eeding and mastodynia
- Impaired liver function. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.
- Information for the Patient, See text of Patient Package Insert below.
- <u>Laboratory Tests.</u> Estrogen administration should generally be guided by clini-cal risponse at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable. For prevention and treatment of osteoporosis however, see Dosage and

D. Drug/Laboratory Test Interactions.

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet court; increased factors il. IVII antigen, IVIII antigen, IVIII coapulant activity, IX. X, XII, VIII-X complex, III-VIII-X com-plex, and beta: thromboglobulin: decreased levels of anti-factor Xa and antithrombin IIII, decreased antithrombin IIII activity, increased evels of tib-rinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound lodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.
- concentrations are unantered. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SBBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged, other pissane proteins may be increased (anglotensinogen/renn substrate, alpha-1-amtitrypsin, cerulonlasmin)
- increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
- Impaired glucose tolerance.
- Reduced response to metyrapone test
- . Reduced serum folate concentration.
- E. Carcinogenesis. Mutagenesis, Impaigned of Fertility. Long term continuous administration of natural and synthetic estrogens in termina nimal species increases are frequency of carcinomas of the breast, uterus, version, veguo. testis, and liver. See Contraindications and Warnings.
- <u>Pregnancy Category X.</u> Estrogens should not be used during pregnancy. See Contraindications and Boxed Warning.
- Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.
- <u>Pediatric Use</u>: Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time have been shown to accelerate epiphysea! closure, resulting in short adult stature if treatment is initiated before the completion of physiologic puberty in y developing children. In patients in whom bone growth is not com-priodic monitoring of bone maturation and effects on epiphyseal center

is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bleeding in girs. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated with estrogen treatment of adults could potentially occur in the pediatric population, including thromboembolic disorders and growth stimulation of certain tumors. Therefore, estrogens should only be administrated to pediatric patients when clearly indicated and the lowest effective dose should always be utilized.

The following additional adverse reactions have been reported with estrogen therapy (see Warnings regarding Induction of neoplasia, adverse effects on the fetus, increased incidence of gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia).

- Genitourinary system
 Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow: breakthrough bleeding, spotting. Increase in size of uterine Vaginal candidiasis.
 Change in amount of cervical
- 2. Breasts
- renormess, enlargement.
 <u>Gastrointestinal</u>
 Rausea, vomiting.
 Abdominal cramps, bloating.
 Cholestatic jaundice.
 Increased incidence of gallbladder disease. 3.
- Skin
 Chloasma or melasma the may persist when drug is discontinued. Erythema multiforme. Erythema modosum. Hemorrhagic eruption. Loss of scalp hair.

- Steepening of corneal curvature intolerance to contact lenses.
- Central Nervous System
 Headache, migraine, dizziness. Mental depression. Chorea.
- Miscellaneous Increase or decrease in weight. Reduced carbohydrate tolerance Aggravation of porphyria. Changes in libido.

- estrogers.

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PRECAUTIONS

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- (2) impairment of glucose tolerance; and
- (3) possible enhancement of mitotic activity in breast epithelial tissue, atthough few epidemiological data are available to address this point (see PRECAUTIONS below).

The choice of progestion, its dose, and its regimen may be important in minimizing these servers effects, but these issues will require further study before they are clarified.

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- 18 ecusive only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to yield statistically significant results, all relevant studies were subject to yield statistically significant results, all relevant studies were subject to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen repeatement thrangy. It may instead have been caused by life-style and medical characteristics of the women shudied with the result that healthier women were selected to estrogen therapy. In general, treated women were of higher socioeconomic and deucational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untrasted women. Although some studies attempted to control for these selection factors, it is common for properfly designed randomized trials to all to confirm benefits suggested by less ripprous study designs. Thus, ongoing and future large-scale randomized trials that sparent benefit.

 [2] Current medical practice often includes the use of concomitant
- tail to confirm this appearant benefit.

 (2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the tavorable effects of estrogens on HDL and LDL levels.
- (3) While the effects of added progestins on the risk of breast cancer are also

- E Carcinopanesis. Mutagenesis, Impaigness, of Fertifity. Long term continuous administration or natural and synthetic estrogens in curves animal species acrosses the frequency of carcinomass of the breast, under a continuous continuous and warrangs.
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- Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly recessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.
- ing mothers has been shown to decrease the quantity and quality of the milk.

 Pediatric Lise: Safety and effectiveness in Bediatric patients have not been established. Large and repeated doses of settogen over an extended period of time have been shown to accelerate epiphysesi closure, resulting in short adult stature if treatment is mitiated before the completion of physiologic pulser in normally developing children. In patients in whom bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended.

is recommended.

Estrogen treatment of prepubertal children also induces premature breast development and vaginal cornification, and may potentially induce vaginal bedoing in girls. In boys, estrogen treatment may modify the normal pubertal process. All other physiological and adverse reactions shown to be associated process. All other physiological and adverse reactions shown to be administed process, and provint instruction of certain lation, including thromboembolic disorders and growth shimulation of certain tumors. Therefore, estrogens should only be administered to pediatric patients when clearly indicated and the lowest effective does should always be utilized.

ADVERSE REACTIONS

The following additional adverse reactions have been reported with estrogen therapy (see Warnings regarding induction of neoplasts, adverse effects on the fetus, increased incidence of galibladder disease, cardiovascular disease, elevated blood pressure, and hypercalcamia).

- Genitourinary system
 Changes in vaginal bleeding pattern
 and abnormal withdrawel bleeding
 or flow; breathrough
 bleeding, spotting,
 increase in size of uterine
 leadmannings
- teiomyomata.
 Vaginal candidiasis.
 Change in amount of cervical secretion.
 Breasts
 Tenderness, enlargement.
- Gastrointestinal
 Nausea, vomiting.
 Abdominal cramps, bloating.
 Cholestatic jaundice.
 Increased incidence of gallbladde
- disease.
 Sain
 Chloasma or melasma that
 may persist when drug is
 discontinued.
 Erythema multiforme.
 Erythema nodosum.
 Hemorrhagic eruption.
 Loss of scalp hair.
 Hisratism.

- Exts.
 Steepening of corneal curvature.

 Intolerance to contact lenses.
- Central Nervous System
 Headache, migraine, dizziness.
 Mental depression.
 Chorea.
- Miscettaneous
 Increase or decrease in weight.
 Reduced carbohydrate toleranc
 Aggravation of porphyria.
 Edema.
 Changes in #bido.

Serious III effects have not been reported following acute legestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vorniting, and withdrawal bleeding may occur in temales.

DOSAGE AND ADMINISTRATION

Estradiol tablets, USP

- For insensent of mederate to severe uspensers symptoms, valval and vagi-nal straphy associated with the mesapesse, the lowest dose and regimes that will sentral symptoms about the chasen and medication should be dis-sentimed as promptly as possible. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

 - The usual initial dosage range is 1 to 2 mg daily of estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Administration should be cyclic (e.g., 3 weeks on and 1 week off).

For treatment of the property of the property

For treatment of breast cancer, for politation only, in appropriately selected unuses and most with metastatic disease.

Suggested dosage is 10 mg three times delly for a period of at least three

4: For treet

for pellination enty.

Suggested dosage is 1 to 2 mg three times daily. The effectiveness of therapy
can be judged by phosphatase determinations as well as by symptomatic

A Commence of the Commence of

For prevention of estimators in the prevent postmenopausal bone loss should be initiated as soon as possible after menopausa. A daily dose of 0.5 mg should be administered cyclically (i.e., 23 days on and 5 days off). The doseap may be educated in the cosape may be educated in the cosape may be disabled in encessary to control concurrent menopausal symptoms. Discontinuation of estrogen replacement therapy may re-establish the

HOW SUPPLIED

Estration tablets, USP 0.5 mg; round, invender colored tablet with bisect, debosed with \P_s and 501. Available in containers of 30 (NDC 51285-501-30), 100 (NDC 51285-501-02). and 501. Available in containers and 500 (NOC 51285-501-04).

Estradiol tablets, USP 1 mg; round, rose colored tablet with bleect, deboseed with \$ and 502. Auditobe in containers of 30 (MDC 51285-502-30), 100 (MDC 51285-502-02), and 502. Available in commons. 500 (NDC 51285-502-04).

Estratiol tablets, USP 1.5 mg; round, aqua colored tablet with bleact, debossed with $\frac{4}{3}$ and 503. Available in containers of 30 (NDC 51285-503-30), 100 (NDC 51285-503-02), and 500 (NDC 51285-503-04).

Estradiol tablets, USP 2 mg; round, blue colored tablet with bisect, di ble in containers of 30 (NDC 51285-504-30), 100 (NDC 51285-504-02), and 500 (NDC 51285-504-04).

Store at controlled room temperature 15°-30°C (59°-86°F).

INFORMATION FOR THE PATIENT

INTRODUCTION

This leaflet describes when and how to use estrogens, and the risks and benefits of

estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doct to be sure you are using the lowest possible does that works, and that you don't use them longer than neces-sary. How long you need to use estrogens will depend upon the reason for use.

1. ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPALISE ("CHANGE OF LIFE").

It you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during preg-nancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urleasy system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing-cancer of the testicles when they become teenagers or young adults

USES OF EXTROGEN

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45 and 55, the ovaries normally stop making estropens. This leads to a drop in
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- To treat cortain conditions in which a young woman's overior do not pro enough extrapon naturally.
- To treat cortain types of abnormal vaginal blooding due to hormonel imbal-ance when your dector has found no serious cause of the blooding.
- To treat cortain concers in special situations, in men and wome
- To provent thinning of bones

To prevent thinning of benea:

Ostooporosis is a thinning of the bones that makes them weaker and allows them to break more assaly. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass start after the menopause. But may strongers after the menopause slows down bone thinning and may prevent bones from breaking. Lifetong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milliparms per day before menopause or 1500 milliparms per day before meno to find out if they are safe for you.

Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopeuse, often because their ovaries were removed during an operation ("surgical memopause"), are more likely to develop osteoporosis than women whose menopause happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During programcy (see Bexed Warning). If you think you may be pregnant, do not use any form of estrogen-containing

During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms, You may have heard that taking estro-gens for years after menopause will keep your stim soft and supple and keep your feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After childhelp or when broadly

Estrogens should not be used to try to stop the Denasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see Dangers of Estrogens, below).

If you are breastleading, you should would using any drugs because many drugs pass through to the baby in the mile. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

user of the uterus. Ir risk of developin Canager at the elevies. Your nick of developing cancer of the uterus gets higher the longer you use estro-gens and the larger doses you use. One study showed that after women stop tak-ring estrogens, this higher cancer risk quickly returns to the usual level of risk if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treat-ment. Because of this risk, IT IS IMPOPITART TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU MEED IT.

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen eas (but see Other Information, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Conser of the brazzi

s have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancel developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used highe doses for shorter time periods. . 4

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Regular breast examinations by a health professional and monthly self-examina-tion are recommended for all women.

Calibladder disease.

Women who use estrogens after menopause are more likely to develop galiblad-der disease needing surgery than women who do not use estrogens.

her usease recording surgery than women who do not use estrogens.

Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more seasily, possibly allowing clotts to form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the heart), a heart aftack (by cutting off blood to the karn), a heart aftack (by cutting off blood to the karn), a pulmonary embolus (by cutting off blood to the kings), or other problems. Any of these conditions may cause death or serious long term disability. However, most studies of low dose estrogen usage by women do not show an increased risk of these complications.

SIDE EFFECTS

addition to the risks listed above, the following side effects have been reported

Naussa and vomiting

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus.

Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

See your dector regularly. While you are using estroo

you are using estrogens, it is important to visit your doctor at least once a writer you are using estrugient, it is improvent to visit your occur at reast order, year for a check-up. If you develop vaginal bleeding while taking estrogens, yo may need further evaluation. If members of your trainly have had breast cancer of you have ever had breast tumps or an abnormal mammogram (breast x-ray) you may need to have more frequent breast examinations.

Response year need for extragens.
You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble

If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, sell your doctor immediately.

Abnormal bleeding from the vacina (possible uterine cancer)

Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts pronthly)

Yellowing of the skin or eyes (possible liver problems)

Pain, pwelling, or tenderness in the abdomen (possible galibladder problem)

OTHER INFORMATION

Estrogens increase the risk of developing a condition (endometrial hyperpla-sia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this con-dition. Therefore, if your uterus has not been removed, your doctor may pre-scribe a progestin for you to take together with the estrogen.

You should know, however, that taking estragens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of HDL blood cho-lesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associate with long-term estrogen use.

Some research has shown that estrogens taken <u>without</u> progestins may pro-tect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estro-gen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect acalies least (fiscase).

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
- H you will be taking calcium supplements as part of the treatment to help prevent osteoporosis, check with your doctor about how much to take.
- Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
- estrogens. If you want more information, set your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians" Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to

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If you have emessal vapines blooding which has not been evaluated by your decire (see Based Warning). Unusual vapinal blooding which has not been evaluated by your decire (see Based Warning) and a warning sign of cancer of the utreux, especially if it happens after menopause. Your doctor must find out the cause of the blooding so that he or she can recommend the proper treatment. Taking estrogers without visiting your doctor can cause you serious harm if your vaginal blooding is caused by cancer of the utreux.

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If you have any chrostation problems.

Estrogen drugs should not be used except in unusually special situations in which your decorar judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see Dangers of Estrogens, below).

Be alort for signs of trauble, it any of these warning signats (or any other unusual symptoms) happen you are using estropeas, and your doctor immediately.

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Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by: Duramed Phermacouticals Cincinnati, OH 45213 USA

CAUTION: Federal law prohibits dispensing without prescrip

DURAMED PHARMACEUTICALS, INC. CINCINNATI, OHIO 45213 U.S.A.

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INFORMATION FOR THE PATIENT





INFORMATION FOR THE PATIENT

INTRODUCTION

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- To treat vulval and vaginal atrophy (litching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause.
- To treat certain conditions in which a young woman's ovaries do not produce enough estrogen naturally.
- To treat certain types of abnormal vaginal bleeding due to norm nce when your doctor has found no serious cause of the bleeding.
- To treat certain cancers in special situations, in men and women.
- To prevent thinning of bones.

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about

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WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During pregnancy (see Boxed Warning).

If you think you may be pregnant, do not use any form of estrogen-containing drug. Using estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.

If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warnings).

Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment. Taking estrogens without visiting your doctor can cause you serious harm if your vaginal bleeding is caused by cancer of the uterus.

If you have had cancer.

Since estrogens increase the risk of certain types of cancer, you should not use estrogens if you have ever had cancer of the breast or uterus, unless your doctor recommends that the drug may help in the cancer treatment. (For certain patients with breast or prostate cancer, estrogens may help.)

If you have any circulation problems.

Estrogen drugs should not be used except in unusually special situations in which your doctor judges that you need estrogen therapy so much that the risks are acceptable. Men and women with abnormal blood clotting conditions should avoid estrogen use (see Dangers of Estrogens, below).

When they do not work.

During menopause, some women develop nervous symptoms or depression. Estrogens do not relieve these symptoms. You may have heard that taking estrogens for years after menopause will keep your skin soft and supple and keep you feeling young. There is no evidence for these claims and such long-term estrogen use may have serious risks.

After childbirth or when breastfeeding a baby.

Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see Dangers of Estrogens, below).

If you are breastleeding, you should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, you should take drugs only on the advice of your health care provider.

DANGERS OF ESTROGENS

Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. One study showed that after women stop taking estrogens, this higher cancer risk quickly returns to the usual level of risk (as if you had never used estrogen therapy). Three other studies showed that the cancer risk stayed high for 8 to more than 15 years after stopping estrogen treatment. Because of this risk, IT IS IMPORTANT TO TAKE THE LOWEST DOSE THAT WORKS AND TO TAKE IT ONLY AS LONG AS YOU NEED IT.

Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (but see Other Information, below).

If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

Cancer of the breast.

Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

Regular breast examinations by a health professional and monthly self-examination are recommended for all women.

Gallbladder disease.

Women who use estrogens after menopause are more likely to develop gall-bladder disease needing surgery than women who do not use estrogens.

Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to the brain), a heart attack (by cut-

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SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use

Nausea and vomiting

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus.

Retention of excess fluid. This may make some conditions worsen, such as asthma. epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

See your doctor regularly.

While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more frequent breast examinations.

Reassess your need for estrogens.
You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble.
If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

(Consider Administration Concern)

Abhormal bleeding from the vagina (possible uterine cancer)

Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)

Yellowing of the skin or eyes (possible liver problems)

Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease);
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Some research has shown that estrogens taken <u>without</u> progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogentreated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

- Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else
- If you will be taking calcium supplements as part of the treatment to help pre-
- vent osteoporosis, check with your doctor about how much to take.

 Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.
- 5. This leaflet provides a summary of the most important information about estrogens. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED

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CAUTION: Federal law prohibits dispensing without prescription

Manufactured by: Cincinnati, OH 45213 USA

Iss. 9/97

Estradio Tablets, USP

INFORMATION FOR THE PATIENT

INTRODUCTION

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must Estrogens have important benefits but also some risks, you must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reason for use.

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR, MENOPAUSE ("CHANGE OF LIFE").

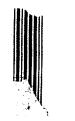
If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

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Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.





USES OF ESTROGEN

(Not every extragen drug is approved for every use listed in this section. If you want to know which of these possible uses are approved for the medicine prescribed for you, ask your doctor or pharmacist to show you the professional labeling. You can also look up the specific estrogen product in a book called the "Physicians' Desk Reference", which is available in many book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.)

To reduce moderate or severe menopausal symptoms.

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Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".

When the astrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have raly mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for

- To treat vulval and vaginal atrophy (itching, burning, dryness in or around the vagina, difficulty or burning on urination) associated with menopause:
- To treat certain conditions in which a young woman's ovaries do not produce enough estrogen acturally.
- To treat certain types of abnormal vaginal bleeding due to hor-monal imbalance when your doctor has found no serious cause of the bleeding.
- To treat certain cancers in special situations, in men and women
- To prevent thinning of bones.

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Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. The bones of the spine, wrists and hips break most often in osteoporosis. Both men and women start to lose bone mass after about age 40, but women lose bone mass faster after the menopause. Using estrogens after the menopause slows down bone thinning and may prevent bones from breaking. Lifelong adequate calcium intake, either in the diet (such as dairy products) or by calcium supplements (to reach a total daily intake of 1000 milligrams per day before menopause or 1500 milligrams per day after menopause), may help to prevent osteoporosis. Regular weight-bearing exercise (like walking and running for an hour, two or three times a week) may also help to prevent osteoporosis. Before you change your calcium intake or exercise habits, it is important to discuss these lifestyle changes with your doctor to find out if they are safe for you. out if they are safe for you.

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Since estrogen use has some risks, only women who are likely to develop osteoporosis should use estrogens for prevention. Women who are likely to develop osteoporosis often have the following characteristics: white or Asian race, slim, cigarette smokers, and a family history of osteoporosis in a mother, sister, or aunt. Women who have relatively early menopause, often because their ovaries were removed during an operation ("surgical menopause"), are more likely to develop osteoporosis than women whose menopause hanners at the average age. happens at the average age.

WHO SHOULD NOT USE ESTROGENS

Estrogens should not be used:

During pregnancy (see Boxed Warning).
If you think you may be pregnant, do not use any form of estrogencontaining drug. Using estrogens while you are pregnant may cause
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After childbirth or when breastfeeding a baby.

Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see Dangers of Estrogens, below).

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SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.

Breast tenderness or enlargement.

Enlargement of benign tumors ("fibroids") of the uterus.

Retention of excess fluid. This may make some conditions worsen, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin, particularly on the face

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

See your doctor regularly.

While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast x-ray), you may need to have more trequent breast examinations.

Reassess your need for estrogens.

You and your doctor should reevaluate whether or not you still need estrogens at least every six months.

Be alert for signs of trouble

If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

Abnormal bleeding from the vagina (possible uterine cancer)

Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

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Manufactured by: Duramed Pharmaceuticals, Inc. Cincinnati, Ok 45213 USA

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Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly) Yellowing of the skin or eyes (possible liver problems)

Pain, swelling, or tenderness in the abdomen (possible galibladder problem)

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia)-that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

You should know, however, that taking estrogens with progestins may have additional risks. These include:

- unhealthy effects on blood fats (especially the lowering of HDL blood cholesterol, the "good" blood fat which protects against heart disease).
- unhealthy effects on blood sugar (which might make a diabetic condition worse); and
- a possible further increase in breast cancer risk which may be associated with long-term estrogen use.

Cated with rong-term estroyen use.

Some research has shown that estrogens taken without progestins may protect women against developing heart disease. However, this is not certain. The protection shown may have been caused by the characteristics of the estrogen-treated women, and not by the estrogen treatment itself. In general, treated women were slimmer, more physically active, and were less likely to have diabetes than the untreated women. These characteristics are known to protect analyst heart disease. against heart disease.

You are cautioned to discuss very carefully with your doctor or health care provider all the possible risks and benefits of long-term estrogen and progestin treatment as they affect you personally.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

Exp. Date:

NDC 51285-501-02

Estradiol
Tablets, USP

(1.5 mg)

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

NDC 51285-501-02

Estradiol
Tablets, USP

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription. 100 Tablets

NDC 51285-502-90
Estradiol
Tablets, USP

CAUTION: Federal law prohibits dispensing without prescription.
30 Tablets

DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA

NDC 51285-502-90

Estradiol
Tablets, USP

CAUTION: Federal law prohibits dispensing without prescription.

DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA



NOC 51285-501-30

Estradiol
Tablets, USP

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription. 30 Tablets

L30528A

NOC 51285-501-30
Estradiol
Tablets, USP 0.5 mg

CAUTION: Federal law prohibits dispensing without prescription. 30 Tablets

DURAMED PHARMACEUTICALS, INC. CINCINNATI, DH 45213 1/8A



Exp. Date:

Lot No.:

Store at controlled room temperature 15°-30°C (59°-88°F). A patient insert should be dispensed with each package.

spense in a tight, light-resistant container as defined the USP. sual Desage: See package insert for complete dosing commendations. DURA med

NDC 51285-501-04 **Estradio/** Tablets, USP

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

This Package is Not Child Resistant Duramed Pharmaceuticals, Inc. Cincinnati, OH 45213 USA

Exp. Date:

Store at controlled room temperature 15°-30°C (59°-86°F).

A patient insert should be dispensed with each package.

sual Decage: See package insert for complete dosing commendations. spense in a tight, light-resistant container as defined in the

DURA med

NDC 51285-502-04 **Estradiol**Tablets, USP



CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets



Exp. Date: Store at controlled noom temperature 15°-30°C (59°-86°F). A patient insert should be dispensed with each package. spense in a tight, light-resistant container as defined in the DURA med Dusage: See package insent for complete dosing NDC 51285-503-04 **Estradiol**Tablets, USP 1.5 mg CAUTION: Federal law prohibits dispensing without prescription.
500 Tablets

This Pectage is not child Resistant Duramed Pharmaceuticals, inc. Cincinnatt, dh 46213 uga

Exp. Date:

Store at controlled room temperature 15°-30°C (59°-86°F).
A patient insert should be dispensed with each package. Dispense in a tight, light-resistant container as defined in the

I Decage: See package insert for complete dosing umendations.

EURA : med NDC 51285-504-04 **Estradiol** Tablets, USP

2 mg

CAUTION: Federal law prohibits dispensing without prescription.
500 Tablets

This Package is Not Child Resistant DURAMED PHARMACEUTICALS, INC CINCINNATI, OH 45213 USA

Exp. Date:

woc 51285-504-30
Estradiol
Tablets, USP
2 mg

CAUTION: Federal law prohibits dispensing without prescription.
30 Tablets

DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA

MDC 51285-504-30

Estradiol
Tablets, USP

2 mg

CAUTION: Federal law prohibits dispensing without prescription.
30 Tablets

DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA



NDC 51285-504-02

Estradiol
Tablets, USP

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

This Package is Not Child Resistant DUTAMED PHARMACEUTICALS, INC. CINCHINATI, DH 45213 USA



NOC 51285-504-02

Estradiol
Tablets, USP

2 mg

CAUTION: Federal law prohibits dispensing without prescription.
100 Tablets

This Package is Ned Child Resistant Durraned Pharmaceuticals, Inc. Cincinnati, OH 45213 USA



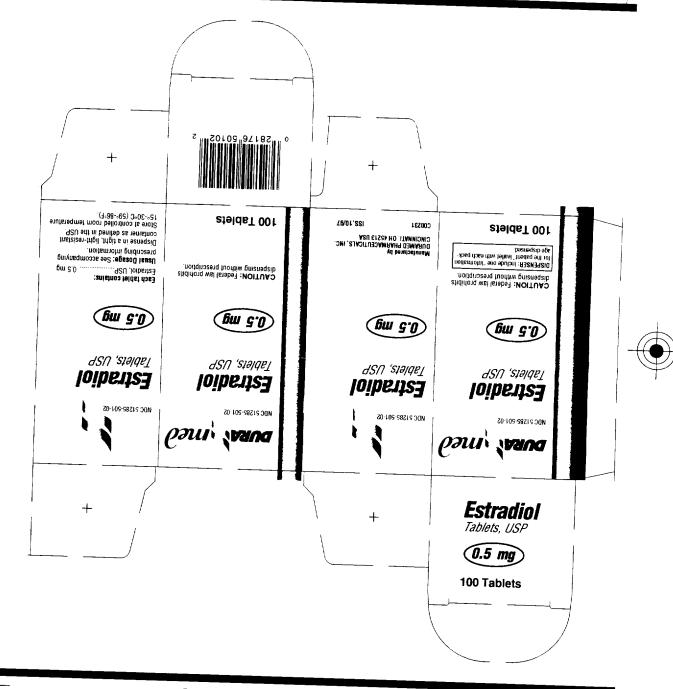
DURA E med This Package is Not Child Resistant Dunamed Pharmaceuticals, INC. Cincinnati, OH 45213 Lisa NDC 51285-503-02 Estradiol Tablets, USP (1.5 mg) CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets Used Desage: See puckage insert for complete Golf, decommendatures. Observes in a tipm, upon-residant container as defined in the USP. Store at controlled crown temperature 15°-30°C, 59°-88°F). A patent insert should be dispensed with each package. pural med This Praisings is Not Child Resistant Duranted Pharmaceuticals, INC. CINCHIMATI, OH 45213 USA NDC 51285-503-02

Estradiol Tablets, USP 1.5 mg
CAUTION: Federal law prohibits dispensing without prescription. 100 Tablets NDC 51285-503-30
Estradiol Exp. Date: DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA Tablets, USP (1.5 mg)
CAUTION: Federal law prohibits dispensing without prescription.
30 Tablets NOC 51285-503-30

Estradiol
Tablets, USP Exp. Date: 1.5 mg CAUTION: Federal law prohibits dispensing without prescription.
30 Tablets DURA Exmed This Package is Not Child Resistant DURANED PLARMACEUTICALS, INC. CINCHINATI, DH 45213 USA NDC 51285-502-02 Estradiol Tablets, USP (1mg) CAUTION: Federal law prohibits dispensing without prescription.

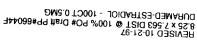
100 Tablets The Pecings is Not Chief Resisted Duramed Physmaceutical S. INC. Cinchinati, DH 46213 USA DUBA E med NDC 51285-502-02 **Estradiol** Tablets, USP (1mg) CAUTION: Federal law prohibits dispensing without prescription. 100 Tablets



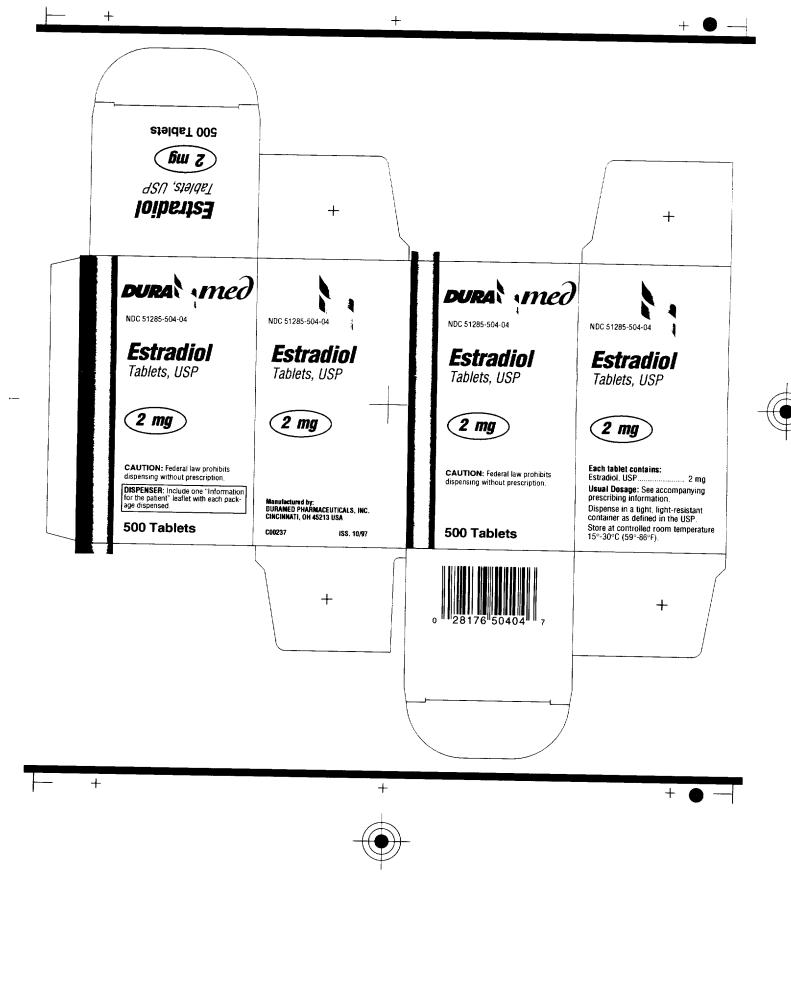


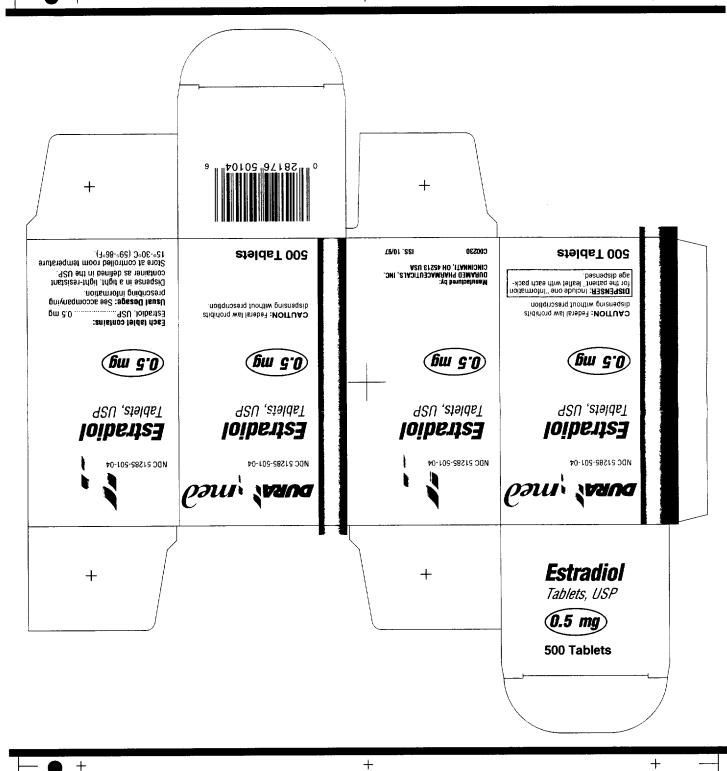












MICTR SREW BLUE BLUE BLUE BLUE



ONBYMED-E21BYDIOF 200 CF 0.2 mg 8 188 X 8 844 @ 100% bO% DBYEL bb% e6041E BEAIZED 10-51-91 10E

















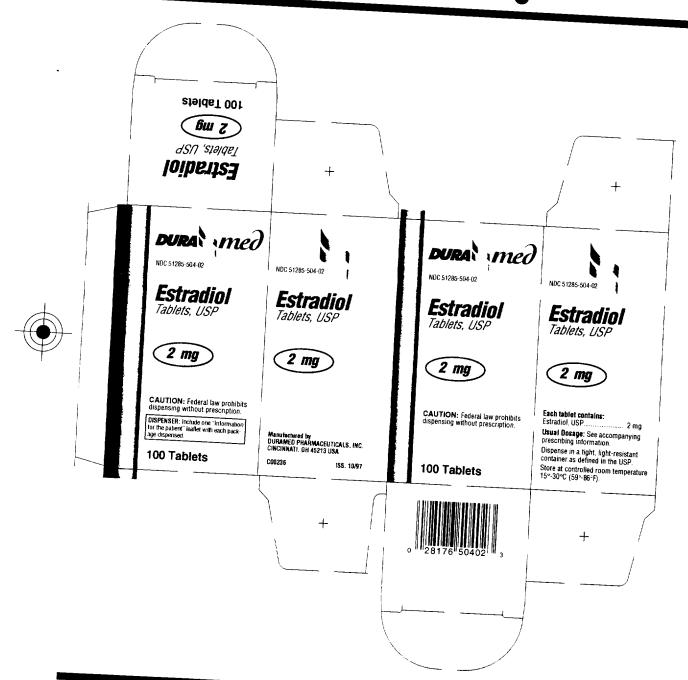


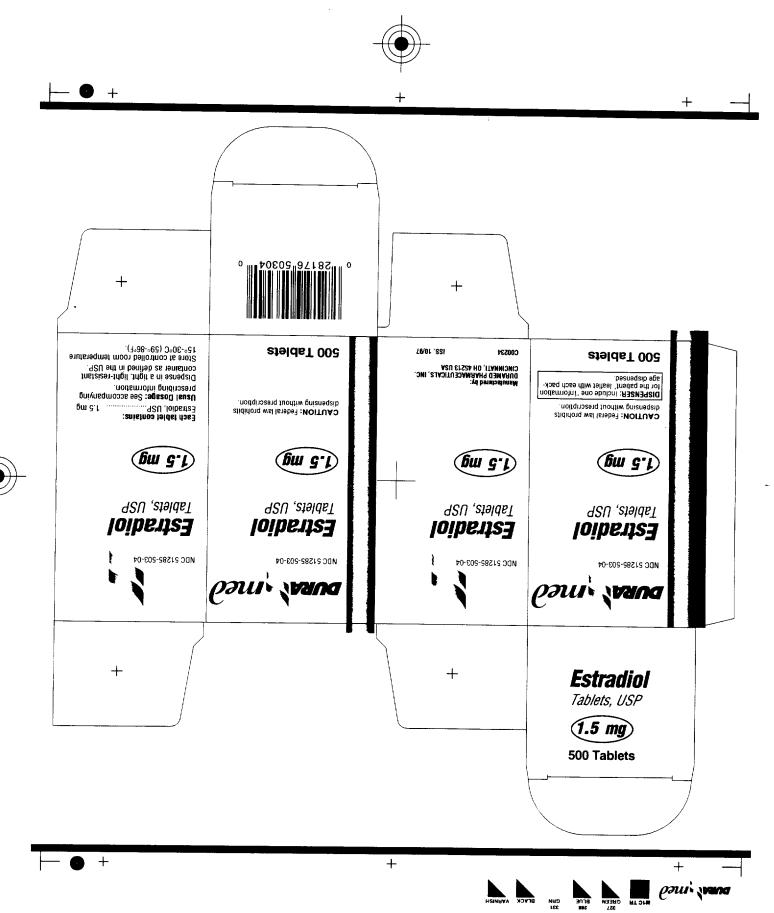


REVISED 10/21/97 JGF 8.25 x 7.563 DIST @ 100% PO#DRAFT PP#66044F DURAMED-ESTRADIOL 100CT 2MG



DURA med 327 GAN 288 BLU 290 BLUE BLACK







REVISED 10-21-97 JGF 8.25 x 7.563 DIST @ 100% PO#DRAFT PP#66044F DURAMED-ESTRADIOL 100CT 1.5MG



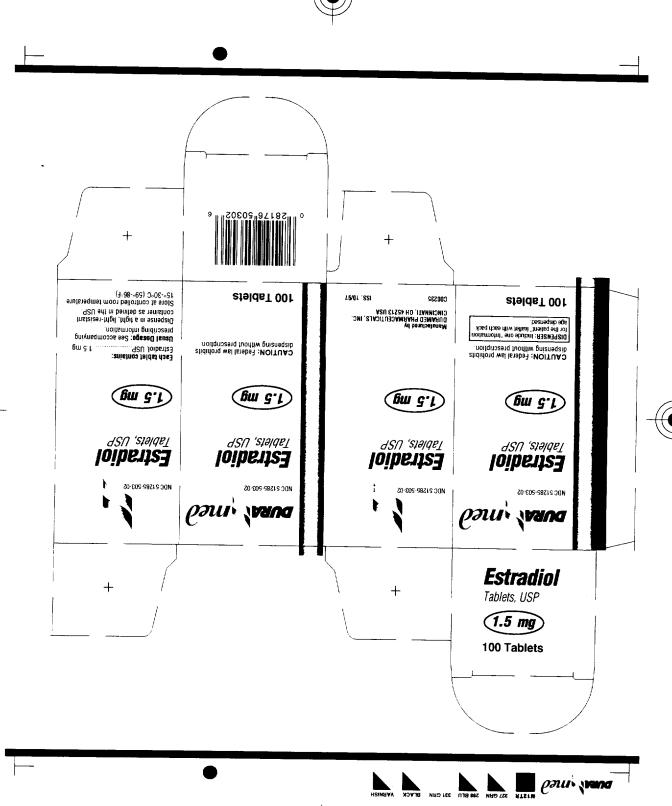
DURAN med 12Th 327 GRN 288 BLU 331 GRN BLACK VARNISH

100 Tablets (gm 2.1) Tablets, USP [estradio] ·med DURA med NDC 51285-503-02 NDC 51285-503-02 NDC 51285-503-02 NDC 51285-503-02 **Estradiol Estradiol Estradiol Estradiol** Tablets, USP Tablets, USP Tablets, USP Tablets, USP (1.5 mg) (1.5 mg) 1.5 mg 1.5 mg **CAUTION:** Federal law prohibits dispensing without prescription. Each tablet contains: Estradiol, USP..... **CAUTION:** Federal law prohibits dispensing without prescription. 1.5 mg Usual Dosage: See accompanying prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F). DISPENSER: Include one "Information for the patient" leaflet with each package dispensed. Manufactured by DURAMED PHARMACEUTICALS, INC. CINCINNATI, OH 45213 USA 100 Tablets 100 Tablets ISS. 10/97

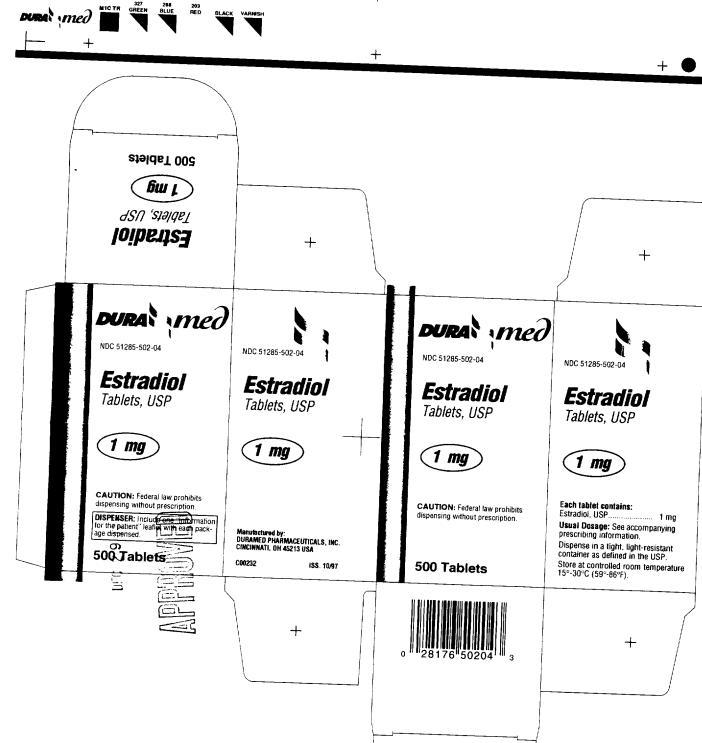






REVISED 10-21-97 JGF 9.188 X 8.844 @ 100% PO# DRAFT PP# 66047F DURAMED-ESTRADIOL 500ct. 1mg





1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040212

CHEMISTRY REVIEW(S)

- 1. CHEMIST'S REVIEW NO.: 4
- 2. ANDA #: 40-212
- 3. NAME AND ADDRESS OF APPLICANT:
 Duramed Pharmaceuticals, Inc.
 5040 Lester Road, Cincinnati, Ohio 45213
- 4. <u>LEGAL BASIS FOR ANDA SUBMISSION</u>: See CR #1
- 5. <u>SUPPLEMENT(s)</u>: N/A
- 6. **PROPRIETARY NAME**: None
- 7. NONPROPRIETARY NAME: Estradiol Tablets, USP
- 8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
- 9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 10/04/96

NC: 10/31/96

Major Amendment: 3/21/97 (Response to NA MAJOR of 03/04/97)
Facsimile Amendment: 9-26-97 (Response to NA letter dated 9-5-97)

- * NC (BIO): 10-17-97 (Response to 9-18-97 bio letter)
- * Minor Amendment (CMC + Labeling): 10-24-97 (Response to

10-17-97 NA letter)

* Amendment (Bio): 11-4-97

FDA:

Acknowledgment letter: 12-9-96

NA (MAJOR) Ltr: 3-4-97 (CR #1 by Shing H. Liu)

NA (Facsimile) Ltr: 9-5-97 (CR # 2 completed by Shing Liu)

Bio deficiency letter: 9-18-97 NA (Minor) Letter: 10-17-97

10. PHARMACOLOGICAL CATEGORY:

Estrogen Replacement

11. Rx or OTC:

Rx

- 12. RELATED IND/NDA/DMF(s):
 - (b)4 Confidential Business

(b)4 - Confidential Business

13. DUSAGE FURM.

Tablets

14. POTENCY:

O.5 mg, 1.0 mg, 1.5 mg, 2.0 mg
[The 1.5 mg tablet is under a suitability petition 993P-0344]

15. CHEMICAL NAME AND STRUCTURE:

See CR #1

16. RECORDS AND REPORTS:

N/A

17. **COMMENTS**:

Duramed has submitted adequate information with respect the chemistry raw materials, release and stability controls and in-process control parameters. Referenced DMF for active material is adequate.

18. CONCLUSIONS AND RECOMMENDATIONS:

Approved pending satisfactory bioequivalence status.

19. **REVIEWER:**

DATE COMPLETED:

Mujahid L. Shaikh

11-20-97

cc:

ANDA 40-212 ANDA DUP 40-212 Division File Field Copy Reading file (for facsimiles only)

Endorsements:

HFD-625/MShaikh HFD-625/Michael Smela/

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F/t by:



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040121

BIOEQUIVALENCE REVIEW(S)



Estradiol Tablets, USP

0.5, 1.0, 1.5, 2 mg

ANDA #40212

Reviewer; Kuldeep R. Dhariwal

File name: 40212SDW.097

Duramed Pharmaceuticals

5040 Lester Road Cincinnati Ohio 45213

Submission Date:
October 17, 1997

November 4, 1997

Response to Review of Bioequivalence Study, Dissolution Data and Waiver Request

Duramed previously submitted a single dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its estradiol 2 mg tablets with Squibb's Estrace® 2 mg tablets (File name: 40212SDW.096). The study was found incomplete and the deficiency comments were sent to the firm. The firm submitted the response as amendment on October 17, 1997 which was assigned to this reviewer on October 29, 1997. The firm was asked on November 3, 1997 to submit the new pharmacokinetic data on diskette for statistical analysis. The firm submitted the diskette on November 4, 1997 which was received by the Office on November 5, 1997.

Response:

Comment 1: For unconjugated estradiol: Please provide all time points used to calculate terminal elimination rate constants. In addition, provide correlation coefficients associated with this determination.

Response: The firm has provided the requested information. The correlation coefficients obtained for calculating terminal elimination rate constants were >0.80 with the following exceptions:

Subject #	Period	Product	Corre. Coefficient
27	III	test	0.761
3	I	reference	0.647
40 .	II	reference	0.761
29	III	reference	0.794

In 14 cases, AUC_{0-inf} could not reliably be calculated (the percentage of extrapolated AUC in these cases were more than 20%). In addition, in 6 cases, there was no recognizable terminal phase and therefore AUC_{0-inf} could not be calculated.

Comment 2: For unconjugated estrone and total estrone: Please provide the following for baseline corrected data: AUC_{0-inf} , terminal elimination rate constant, terminal elimination half-life, AUC_{0-inf} ratios, and statistical analysis of AUC_{0-inf} data. Time points used to calculate terminal elimination rate constant and the correlation coefficients should also be provided.

Response: The firm has provided the requested information.

Unconjugated estrone: AUC_{0-inf} could not be calculated for subject #21, period III, reference product because there was no recognizable terminal phase. The correlation coefficients obtained for calculating terminal elimination rate constants were >0.80 with the following exceptions:

Subject #	Period	Product	Correl. Coefficient
4	I	test	0.787
24	I	test	0.747
30	II	test	0.731
35	II	test	0.764
4	III	test	0.777
16	III	test	0.703
7	I	reference	0.741
30	I	reference	0.743
35	I	reference	0.743

The 90% confidence intervals for AUC_{0-inf} were 100.99-111.84% as calculated by QMR staff (report attached). AUC_{0-inf} ratios in all cases were above 0.80.

Total estrone: The correlation coefficients obtained for calculating terminal elimination rate constants were >0.857. $AUC_{0-t}/AUC_{0-inf} \text{ ratios in all cases were above 0.80. The 90% confidence intervals for <math display="block">AUC_{0-inf} \text{ calculated by QMR staff were as follows (report attached):}$

including all subjects: 91.63-103.13%

excluding subjects #4,13,19, and 22 as their first measurable plasma concentration was C_{max} : 91.58-104.18%

Comment 3. For total estrone, subject #5 samples: page 684 extraction date: 13.05.1996 analysis date: 09.05.1996 Please clarify.

Response: The firm states that the extraction date given in the report was a typographical error. The correct date of the extraction is 08.05.1996, i.e. the day before analysis.

Comment 4. Some of the samples for total estrone were analyzed 6 days after extraction. How were the samples for total estrone stored after extraction? What is the stability of total estrone in these samples? What is the room temperature stability of extracted samples for total estrone?

Response: Total estrone is hydrolyzed prior to extraction to the unconjugated estrone. Thus, only unconjugated estrone is contained in the extraction solvent. The extracts were stored in a refrigerator at 5°C. Unconjugated estrone in the extraction solvent is stable for at least 6 days at <13°C and for at least 24 hours at room temperature.

Comment 5: Please provide individual values of all determinations for extraction recovery of unconjugated estradiol (n=4), unconjugated estrone (n=4) and total estrone (n=6) at each concentration tested.

Response: The firm states that the validation report incorrectly stated n=4 for unconjugated estradiol and unconjugated estrone. In fact, at each concentration the recovery was determined only 3 times. The firm has provided the individual values.

(b)4 - Confidential Business

Comment 9: Please submit SOP's for analytical methods.

Response: The firm has submitted SOP's.

Comments:

- 1. The firm has provided the AUC_{0-inf} data for unconjugated estrone and total estrone. The 90% confidence intervals are within the acceptable limits of 80-125%.
- 2. The firm has repeated extraction recoveries of unconjugated estradiol and unconjugated estrone. The new results give satisfactory extraction recoveries, however they differ from the original method validation test results. One wonders why the firm has now got very consistent results. It may also be noted that during the course of study sample analysis, the % recovery and precision of standard and quality control samples was quite good. The reviewer discussed these discrepancies and the firm's other responses with the team leader and the reviewer agrees with team leader's recommendation to accept the arguments given by the firm.
- 3. The firm repeated the stability of extracted unconjugated estradiol and unconjugated estrone stored at room temperature for 48 hours. The new results show a relative concentration of 94.1% at 5 pg/mL unconjugated estradiol compared to 77% reported earlier. Again, the new results are much better.
- 4. The firm has otherwise satisfactorily responded to all the deficiencies.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Duramed Pharmaceuticals on its estradiol 2 mg tablets, lot #C-0016 comparing it to the reference listed drug Estrace 2 mg tablets, lot #MMD 99 manufactured by Bristol-Myers Squibb has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Duramed's estradiol 2 mg tablets are bioequivalent to the reference product Estrace 2 mg tablets manufactured by Bristol-Myers Squibb.

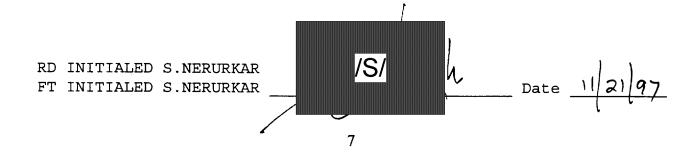
- 2. The dissolution testing conducted by Duramed on its estradiol 0.5, 1.0, 1.5, and 2 mg tablets are acceptable. The firm has conducted an acceptable in vivo bioequivalence study comparing its 2 mg tablets of the test product with 2 mg tablets of the reference product Estrace manufactured by Bristol-Myers Squibb. The formulations for the 0.5, 1.0, and 1.5 mg tablets are proportionally similar to the 2 mg tablet which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 0.5, 1.0, and 1.5 mg test tablets is granted. The 0.5 and 1.0 mg tablets of the test product are therefore deemed bioequivalent to the 0.5 and 1.0 mg tablets of Estrace manufactured by Bristol-Myers Squibb. The waiver of in vivo bioequivalence study requirements for Duramed's 1.5 mg tablet is granted based on the approved suitability petition filed by Bristol-Myers Squibb for 1.5 mg tablet.
- 3. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 500 mL of 0.3% sodium lauryl sulfate at 37°C using apparatus II (paddle) at 100 rpm. The test products should meet the following specifications:

Not less than (b)4Q) of the labeled amount of estradiol in the dosage form is dissolved in 60 minutes.

4. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.



Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence



Addendum to Statistical Report, June 25, 1997
EstroplaceTM (estradiol tablets, USP); Office of Generic Drugs ANDA 40-212, Duramed Pharmaceuticals, Inc. OGD reviewer: Kuldeep Dhariwal

The applicant conducted a three period crossover study with 40 subjects to assess the bioequivalence between the reference product, 2mg Estradiol Tablets, USP, Estrace, Bristol-Myers Squibb, and the test product, 2 mg Estradiol Tablets, USP, Duramed. Three plasma concentrations were measured, sum of conjugated and unconjugated estrone "total estrone", unconjugated estrone "free estrone", and 17-β estradiol "free estradiol".

In the original submission, the applicant did not include the endpoint the area under the plasma concentration time curve from zero to infinity, AUCinf, for two of the plasma levels, total estrone and free estrone. This addendum contains the statistical analysis of AUCinf for these two plasma levels.

Study design

This study is a two treatment, three period, four sequence design with 40 subjects. The reference product (R) is Estradiol Tablet, USP, 2mg (Estrace, Bristol-Myers Squibb), 1x1 tablet of 2mg Estradiol. The test product (T) is Estradiol Tablet, USP, 2 mg (Duramed), 1x1 tablet of 2mg Estradiol. The four sequences are TRT, TRR, RTT, and RTR.

The Model

Both models of the log transformed AUCinf included covariates sequence, period, and treatment and contained a random effect for subject and a random subject-by-formulation interaction. Since this substance occurs endogenously a carryover-by-treatment effect was included in the initial model. For total estrone this effect was found to be significant and was included in the final model. For free estrone this effect was not significant and was dropped from the model.

SAS Code for free estrone:

proc mixed;

class seq subj per trt;

model lnauci = seq per trt /solution;

random trt / subject=subj type=un solution g;

lsmeans trt/cl pdiff alpha=.1;

run;

Results of Analysis

The OGD reviewer requested that a few models be run with certain subjects dropped from the analysis. For free estrone, models were run with all available data. For total estrone, models were run with all available data and again with Subjects 4, 13, 19, and 22 omitted.

The parameters and 90% confidence intervals for the endpoints, back-transformed, are given in the table below. The first column states the drug/metabolite that was measured and the

ANDA 40-212, Estradiol Tablets, USP, Duramed Pharmaceuticals, Inc., November 7, 1997

pharmacokinetic endpoint. The second column lists which subjects were analyzed. Column 3 gives the estimated difference between test and reference in log scale (Mdiff) with its corresponding standard error (SE). Columns 4 and 5 give the estimated ratio and 90% confidence interval back-transformed. Column 6 states whether it passed or failed the BE criterion.

Compound and Metric	Subjects	Mdiff (SE)	Estimated Ratio	90% Confidence Interval	Pass or Fail
Free Estrone					
AUCinf	all available data	0.0609 (0.0306)	1.0628	1.0099, 1.1184	Pass
Total Estrone					
AUCinf	all available data	-0.0283 (0.0354)	0.9721	0.9163, 1.0313	Pass
AUCinf	4,13,19,22 omitted	-0.0235 (0.0386)	0.9768	0.9158, 1.0418	Pass

Conclusions

Confidence intervals for AUCinf for both free and total estrone were contained within the regulatory boundaries. The difference between our interval of AUCinf for total estrone and that of the sponsor is due to our inclusion of carryover effects in the model.

/S/

Karen M. Higgins, Sc.D. Staff Fellow, QMR November 7, 1997

Concur:_ /S/ 11/7/97

Donald J. Schuirmann, Acting Director QMR

ANDA 40-212, Estradiol Tablets, USP, Duramed Pharmaceuticals, Inc., November 7, 1997

cc:

Original ANDA 40-212

HFD-655 Kuldeep Dhariwal

HFD-615 Harvey Greenberg

HFD-705 QMR Chron HFD-705 Karen Higgins

HFD-705 Donald Schuirmann